A COMPARATIVE STUDY OF LOW DOSES OF INTRATHECAL KETAMINE AND MIDAZOLAM WITH BUPIVACAINE FOR INFRAUMBILICAL SURGERIES

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BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled "**A COMPARATIVE STUDY OF LOW DOSES OF INTRATHECAL KETAMINE AND MIDAZOLAM WITH BUPIVACAINE FOR INFRAUMBILICAL SURGERIES"** is bonafide record work done by **DrC.KARPAGAVALLI** under my direct supervision and guidance, submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for MD, Branch X –Anaesthesiology.

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DECLARATION

I **Dr.C.KARPAGAVALLI** solemnly declare that this dissertation titled **"A COMPARATIVE STUDY OF LOW DOSES OF INTRATHECAL KETAMINE AND MIDAZOLAM WITH BUPIVACAINE FOR INFRAUMBILICAL SURGERIES"** has been done by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of Doctor of Medicine degree Branch –X (Anaesthesiology) to be held in March 2010.

Place : Madurai **Dr.C. KARPAGAVALLI**

Date :

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CONTENTS

INTRODUCTION

“Primum Non Nocere”

(First of all do no harm)

-THOMAS SYDENHAM

The term “Spinal Anaesthesia” was coined by Leonard Corning in 1885.

In 1898, the first deliberate spinal anaesthesia was given to August Karl Gustav Bier by his assistant Dr.Hildebrandt. The second attempt was done on the theca of Dr.Hildebrandt. Twenty three minutes after the injection of cocaine, Dr. Bier noted “A strong blow with an iron hammer against the tibia was not felt as pain.”

The simplicity of the technique of spinal anesthesia and its reliability had made it one of the preferred techniques in infraumbilical surgeries.

Bupivacaine when used alone intrathecally produces analgesia for three to four hours, making it unsuitable in cases where the duration of surgery is longer.

Different adjuvants such as opioids, clonidine or neostigmine may be added to enhance spinal anesthesia, though their use is limited because of side effects.

Ketamine is a potent analgesic acting as an antagonist at N-Methyl – D asparticacid receptor sites and has a local anaesthetic action. Intrathecal ketamine has been used as a sole agent or in combination with local anaesthetics. It provides stable haemodynamics but shorter duration of action.

Midazolam has a spinally mediated antinociceptive effect and enhance the analgesic effect of local anaesthetics when used intrathecally. It improves the duration and quality of the spinal anaesthesia, though it does not prevent the haemodynamic instability produced by intrathecal bupivacaine.

Hence this study is done to evaluate the effect of small doses of ketamine and midazolam with bupivacaine intrathecally in terms of duration and quality of analgesia and side effect profile.

AIM OF STUDY

The aim of this study is to evaluate the effect of low doses of ketamine and midazolam with bupivacaine intrathecally in terms of duration of analgesia and haemodynamic parameters.

ANATOMY OF SUBARACHNOID SPACE

Subarachnoid block means the temporary interruption of nerve transmisssion within the subarachnoid space produced by injection of a local anaesthetic solution into cerebrospinal fluid.

Applied anatomy of vertebral canal:

Vertebral canal extends from foramen magnum to the sacral hiatus. It protects the spinal cord.

The vertebral column comprises 33 vertebrae (7-cervical, 12-thoracic, 5-lumbar, 5-fused sacral and 4-coccygeal) has four curves. Cervical and lumbar curves are convex anteriorly and thoracic & sacral curves are convex posteriorly. The curves of the vertebral column influences the spread of the local anaesthetic in the subarachnoid space.

Each vertebra is composed of a body separated from the adjacent vertebra by intervertebral disc and formed by pedicles and laminae, which surround and protect the cord laterally and posteriorly.

The vertebral column is bound together by several ligaments. They are,

1. Supraspinal ligament – passes longitudinally over the tips of the spinous processes from C7 to the sacrum.
2. Interspinous ligament – connects the adjoining spinous processes together.
3. Ligamentum Flavum – composed of yellow elastic fibres known as yellow ligament, connects the adjacent laminae. They become progressively thicker from above downwards.
4. Posterior longitudinal ligament – It is on the posterior surface of bodies of vertebrae.
5. Anterior longitudinal ligament – It runs along the front of the vertebral bodies.

There are seven projections from these vertebral (or) neural arches. They are,

a) Three muscular processes–(2-Transverse processes, 1-spinous process for the attachment of muscle and ligaments).

b) Four articular process – Two upper & two lower which in the lumbar region prevent rotation but allow limited flexion and extension between continuous vertebrae.

Vertebral canal formed by these structures has deficiencies posteriorly in the midline called inter laminar foramina which enlarge in flexion accessible for the passage of spinal needle. The direction of spinous process determine the direction of spinal needle.

SPINAL CORD:

It is the direct continuation of the medulla oblongata extending from the upper border of the atlas to the first lumbar vertebra below which there is leash of nerve roots termed cauda equina. Spinal nerves are 31 pairs totally.

8 – Cervical

12 – Thoracic

5 – Lumbar

5 – Sacral

1 – Coccygeal

Each of the spinal nerve is composed of anterior and posterior roots uniting at the inter vertebral foramina and form a nerve trunk. Membranes covering the spinal cord are dura mater, arachnoid mater and piamater. Dura and arachnoid mater end at S_2 level. Piamater is closely applied to the spinal cord.

BLOOD SUPPLY:

It is from the anterior spinal artery which is a branch of vertebral artery and also by a pair of posterior spinal arteries which arise from the posterior inferior cerebellar arteries. There is no anastamosis between these arteries.

SPINAL VEINS:

The spinal veins are arranged into anterior and posterior plexus which are draining into vertebral, azygos and lumbar veins.

CEREBROSPINAL FLUID:

This is an ultrafiltrate of the blood plasma from choroid plexus of the lateral ventricles with a pH of 7.32 (7.27-7.37)

It is a clear, colourless fluid found in the cranial and spinal subarachnoid spaces and in the ventricles of the brain.

The total volume of CSF in an average adult ranges from 120-150ml of which 25-35ml is in the spinal subarachnoid space.

Composition of cerebrospinal fluid:

Specific gravity	-	1.006 (1.003-1.009) at 37^0C
Pressure	-	60-80mm of water
Pco_2	-	48mmHg
$HCo3^-$	-	23meq/l

Na^+	-	133-145meq/l
Ca^+	-	2-3meq/l
$Po4^-$	-	1.6mg/dl
Mg^+	-	2-2.5mg/dl
cl^-	-	15-20mg/dl
Protein	-	23-38mg/dl
Sugar	-	45-80mg/dl
Lymphocytes	-	0-5cells/cmm

An important factor that determine the spread of drug in cerebrospinal fluid is the specific gravity of the drug in relation to that of cerebrospinal fluid (Baricity) which is 1.003-1.009. Hyper baric solution is one which is denser than CSF at 37^0C.

PHYSIOLOGY OF SUBARACHNOID BLOCK

Subarachnoid block implies the temporary interruption of nerve transmission within the subarachnoid space by injections of local anaethetics. The blockade of nerve fibres occur in the order of temperature, pain, proprioceptive and then motor fibres.

FACTORS INFLUENCING HEIGHT OF BLOCKADE:

a - Site of injection

b - Angulation of needle

c - Characteristic of local anaesthetic - baricity

d - Dose of local anaesthetic

e - Position of the patient during and after injection

f - Anatomic configuration of spinal column.

g - Patient height (at extrems)

h - Volume of cerebrospinal fluid

i - Reduced cerebrospinal fluid with increased intra abdominal pressure (eg. Pregnancy)

a) Effects on Cardio Vascular System:

Most important physiological response to subarachnoid block involve cardio vascular system due to combined effect of autonomic denervation, higher level of neural block, added effect of vagal innervation.

Local anaesthetics and vasoactive substances administered in small doses intrathecally leads to direct cardiovascular effect.

Level of sympathetic denervation determines the magnitude of cardio vascular system responses, but the relationship is neither predictable nor precise.

Sympathetic denervation produces arterial and more physiologically important arteriolar dilatation and vasodilatation in the venous circulation produces fall in blood pressure.

Due to Bainbridge reflex, the fall in blood pressure is associated with bradycardia, blockade of cardiac sympathetic fibre from T1-T4 is an additional factor that causes bradycardia.

b) Effects on Respiratory System:

Respiration is not depressed normally. High spinal can cause paralysis of intercostals muscles but resting tidal volume, maximum inspiratory volume, respiratory rate, arterial blood gas, negative

intrapleural pressure and also the phrenic nerve are unaffected. Hypoxia may accompany hypotension and is corrected by oxygen administration via face mask.

c) Gastro Intestinal Effect:

Preganglionic fibres from T_5-L_1 are inhibitory to gut. So in sympathetic blockade the small intestine contracts with relaxed sphincters and peristalsis remains normal. Handling of viscera causes discomfort and bradycardia since vagus is not blocked.

d) Hepatic and Renal Effects:

The hepatic blood flow decreases and is directly proportional to the decrease in blood pressure. There may be normal hepatic oxygen extraction. Renal blood flow is maintained by autoregulation and does not decrease till mean arterial pressure goes below 50mmHg.

e) Genito Urinary System:

Sphincters of bladder are not relaxed, and tone of the ureter is not greatly altered. Urinary retention occurs. Penis is often engorged. Uterine tone is unchanged in pregnancy. In the absence of hypotension spinal anaesthesia has got no effect on the progress of labour and uterine blood flow.

f) Metabolic and hormonal effect:

Spinal anaesthesia blocks hormonal and metabolic responses to nociceptive stimuli arising from the operative site. It minimizes the rise in blood sugar, cortisol, catecholamines, renin and aldosterone release associated with stress. Post operative negative nitrogen balance and secretion of antidiuretic hormone are inhibited.

g) Thermo Regulation:

Hypothermia results from heat loss to the cold environment due to vasodilatation.

PHARMACOLOGY OF DRUGS

a) Bupivacaine:

Bupivacaine is an amide linked local anaesthetic. It is a hydrochloride salt of d(1)-1-butyl N-(2'6' dimethylphenyl) piperidine – 2 - carboxamide and is presented as a racemic mixture.

- It was synthesized by EO af Ekenstem.
- First reports of its use was published in 1963 by Telivuo.
- It is derived from Mepivacaine and is very stable compound and may be autoclaved repeatedly.

Pka is 8.1

MW	-	288
Protein binding	-	95%
Lipid solubility	-	28
Elimination half life	-	210 minutes
Toxic plasma concentration	-	>1.5µg/ml
Approximate duration of action	-	175minutes

Availability:

Ampoule - 0.5% Bupivacaine hydrochloride 4cc

0.5% Bupivacaine hydrochloride with dextrose (heavy) 4cc

Vials - 0.25% and 0.5% Bupivacaine hydrochloride 20cc

Dosage - Maximum dosage 3mg/kg body weight.

Uses:

- Spinal anaesthesia
- Epidural anaesthesia
- Caudal anaesthesia
- Continuous epidural anaesthesia
- Peripheral nerve block

Onset time and duration of action

Site of action	Onset (minutes)	Duration (minutes)
Intrathecal	5	180-240
Epidural	15-20	165-225
Brachial plexus	15-20	600

Pharmacokinetics:

Once injected intrathecally, it gets absorbed by the nerve rootlets and results in the desired effect. It is rapidly absorbed from the site of injection, but the rate of absorption depends on the vascularity at the site and presence of vasoconstrictors.

High lipid solubility of bupivacaine makes it easy for nerve and vascular tissue penetration.

80-95% of the absorbed bupivacaive binds to the plasma.

Distribution:

Rapid distribution phase: (α)

In this phase the drug is distributed to highly vascular region $t1/_2$ of α - being 2.7 minutes.

Slow disappearance phase: (β)

In this phase the drug distributes to slowly equilibrating tissues $t1/_2$ of β – being 28minutes.

Biotransformation and excretion phase δ

$T1/_2$ of δ is 3.5hours and clearance is 0.47 litre/minute.

Biotransformation:

Possible path ways of metabolism of bupivacaine include aromatic hydroxylation and conjugation. Only the N-dealkylated metabolite, N-desbutyl bupivacaine has been measured in blood (or) urine after epidural (or) spinal anaesthesia. Alpha1 acid glycoprotein is the most important plasma protein binding site of bupivacaine and its concentration is increased by many clinical situations including post operative trauma.

Excretion:

It is through the kidney, 4-10% of the drug is excreted unchanged.

Mode of Action:

a) Site of action:

i) The spinal nerve rootlet fine nerve filaments having a large surface area are exposed to the local anaesthetics.

ii) Posterior and lateral aspects of the spinal cord itself.

b) Sodium Channel blockade:

They impede sodium ion access to the axon interior by occluding the transmembrane sodium channels thus delaying the process of depolarisation and axon remains polarized. It is a non-depolarisation blockade.

Pharmacodynamics:

It has got a longer duration of action but a slower onset.

Cardio vascular system:

It reduces cardiac output by reducing the sympathetic tone, by slowing the heart rate and by reducing the venous return, it produces a fall in arterial blood pressure but it is relatively slow and is seldom very profound.

It produces a fall in central venous pressure. It causes an increase in lower limb blood flow and reduction in incidence of deep vein thrombosis.

Respiratory System:

Spinal blockade seldom, if ever causes respiratory problem.

Gastro intestinal tract:

There is an increase in gastro intestinal motility and emptying of the gastric contents are better.

Toxicity:

Toxicity is related to plasma level of unbound drug and more likely due to an inadvertent intravenous injection. Systemic toxicity reactions primarily involve central nervous system and cardio vascular system. The blood level required to produce central nervous system toxicity is less than that required to produce circulatory collapse.

Central Nervous System Toxicity:

Initial symptom includes feeling of light headedness and dizziness, followed by visual and auditory disturbances. Objective signs are excitatory and includes shivering, muscle twitching and tremor. Ultimately generalized tonic, clonic seizures occurs.

Cardiovascular System Toxicity:

The rate of depolarization in fast conducting tissue of purkinje fibres and ventricular muscle is decreased. The rate of recovery of

bupivacaine induced block is slower than that of lignocaine. Extremely high concentration of the drug causes sinus bradycardia and cardiac arrest.

PHARMACOLOGY OF KETAMINE

History :

Ketamine was synthesized in 1962 by Stevens and was first used in human in 1965 by Corssen and Domino. Ketamine differs from most other drugs used to induce anaesthesia because it has a significant analgesic effect. Ketamine has 2 stereoisomers, S(+), and R (-). The S(+) is more potent and is associated with fewer side effects. Ketamine is a phencyclidine derivative.

Physicochemical Characteristics :

Ketamine has a molecular weight of 238 KD, is partially water soluble with a PK of 7.5.

Mechanism of action :

Ketamine binds non competitively to the phencyclidine recognition site on N-methyl D-aspartate (NMDA) receptors. Ketamine may exert effects at other sites including opioid receptors, monoaminergic receptors, muscarinic receptors and voltage – sensitive sodium and L type calcium channels.

NMDA Receptor Antagonism :

Ketamine inhibits activation of NMDA receptors by glutamate, decreases the presynaptic release of glutamate and potentiates the effects of inhibitory neurotransmitter GABA.

Opioid receptors :

Ketamine has been reported to interact with mu, delta, and kappa opioid receptors.

Sodium channels :

Consistent with its mild local anaesthetic like properties ketamine interacts with voltage gated sodium channels.

Muscarinic receptors :

Ketamine has an antagonist effect at the muscarinic receptors.

Mono aminergic receptors :

The antinociceptive action of ketamine may involve descending inhibitory monoaminergic pathways.

PHARMACOKINETICS

Ketamine has a rapid onset of action, relatively shorter duration of action and high lipid solubility. Peak plasma concentrations of ketamine occur within 1 minute after iv administration and within 5 minutes after intramuscular

administration. Ketamine has a high hepatic clearance rate (1litre /minute) and a large volume of distribution (3 litres / kg) resulting in an elimination half time of 2-3 hrs.

CLINICAL USES :

1. ANALGESIA

- Ketamine is a unique drug evoking intense analgesia at subanaesthetic doses.
- The analgesic effects of ketamine are primarily due to its activity in the thalamic and limbic systems, which are responsible for the interpretation of painful signals.
- Small doses of ketamine are also useful adjuvants to opioids analgesia
- Spinal cord sensitization is responsible for pain associated with touching or moving an injured part.
- Control to the development of spinal cord sensitization in the spinal cord dorsal horn.

2. Neuraxial Analgesia :

- Epidural or intrathecal administration of ketamine produces analgesia without depression of ventilation.

- The affinity for spinal opioid receptors may be 10,000 fold weaker than that of morphine.
- Intrathecal administration of ketamine produces variable and brief analgesia.

3. Induction of Anaesthesia :

Administration of 1-2 mg/kg IV on 4-8mg/kg IM injection of ketamine produces induction of anaesthesia. Consciousness is lost in 30-60 seconds after IV administration and in 2 to 4 minutes after IM injection. Ketamine is a beneficial drug for induction in patients with hypovolemia and bronchial asthma.

4. Sedation :

Ketamine in subanaesthetic dose (<1.0mg/kg) is used for sedation.

SYSTEMIC EFFECTS :

Central nervous system :

1. Ketamine increases cerebral blood flow and cerebral metabolic rate and oxygen consumption.
2. Ketamine increases intracranial pressure. Prior administration of thiopental, diazepam, midazolam has been shown to blunt ketamine induced cerebral blood flow.

3. Ketamine's effect on EEG are characterized by abolition of alpha rhythm and dominance of theta activity.

Cardiovascular system :

1. Ketamine produces cardiovascular effects that resemble sympathetic nervous stimulation. A direct negative inotropic effect is usually over shadowed by central sympathetic stimulation.

Ventilation and Airway :

1. The ventilatory response to carbondioxide is maintained during ketamine anaesthesia and the PaCO2 is unlikely to increase > 3mm Hg.
2. Apnea can occur if the drug is administered rapidly by intravenous route,
3. Upper airway reflexes remain relatively intact.
4. Salivary and tracheobronchial mucous gland secretions are increased by IV or IM administration of ketamine.

Bronchomotor Tone :

Ketamine has bronchodilatory activity. Ketamine has been used in subanesthetic doses to treat bronchospasm in the operating room and intensive care unit.

Uses of doses of ketamine :

Induction of General anaesthesia :

0.5- 2 mg / kg IV

4 – 6 mg / kg IM

Maintenance of General anaesthesia

0.6- 1 mg / kg IV

15 - 45 mg/kg / min IV with N2O inO2

30 – 90 mg/kg / min IV without N2O

Sedation and Analgesia :

0.2 – 0.8 mg / kg IV over 2-3 min

2 – 4 mg / kg IM

Preemptive / Preventive analgesia

0.15 – 0.25 mg / kg IM

Side effects and Contraindications :

1. Ketamine produces emergence reactions. Common manifestation are vivid dreaming, extra corporeal experiences and illusions. These incidents are often associated with excitement, confusion, euphoria and fear.
2. Ketamine increases cerebral blood flow and is contraindicated in patients with raised intracranial pressure.

3. It is contraindicated in patients with open eye injury or other conditions with raised intraocular pressure.
4. Ketamine's preservative chlorbutanol is neurotoxic
5. Ketamine is avoided in patients with psychiatric disease.

PHARMACOLOGY OF MIDAZOLAM

Midazolam is an imidobenzodiazepine, water soluble benzodiazepine. Benzodiazepines were introduced in early 1960s. Diazepam, the most popular drug of this group for the past 2 decades, is water insoluble, has a prolonged effect and is painful during injection. The unique chemical structure of midazolam confers a number of physicochemical properties that distinguish it from other benzodiazepines. This drug was synthesized in 1976 by Tryer and walser.

CHEMISTRY:

Benzodiazepines are so called because they consist of a benzene ring fused with a seven member diazepine ring. Various modification in the structure of the ring systems have yielded compounds with similar activities.

Midazolam with molecular weight of 362, has a fused imidazole that is different from classic benzodiazepines. The imidazole ring accounts for the stability of an aqueous solution and rapid metabolism. The ring exhibits a pH dependent ring opening phenomenon. The ring opens at pH less than 4 making the drug

soluble in aqueous solution. Once midazolam enters the body, the pH changes to 7.4 and drug assumes closed ring structure and becomes highly lipid soluble. Midazolam is the most lipid soluble benzodiazepine.

PHARMACOKINETICS:

Midazolam is rapidly absorbed from gastro intestinal tract, but only 50% of the orally administered drug enters the circulation, as substantial portion is metabolized during the first hepatic flow. Thus the oral dose is twice as high as intravenous dose.

Peak plasma concentrations are seen within an hour of ingestion. When given intramuscularly, the absorption is more predictable than diazepam. Being highly fat soluble it crosses blood brain barrier more easily than diazepam, to gain access to the receptors. It has a more rapid onset of action. After intravenous administration of midazolam to healthy adults the disappearance of midazolam from the plasma proceeds in two distinct phases. The initial phase of rapid disappearance is principally due to distribution of the drug while the final and slower phases of disappearance is attributable mainly to biotransformation. The volume of distribution of midazolam averages between 1 and 2.5 1/kg. Midazolam is tightly

bound to plasma protein. After distribution equilibrium is reached, elimination half-life varies from 1 to 4 hours. Midazolam is metabolized mainly by hepatic microsomal oxidative mechanism, by a process of hydroxylation. The fused imidazole ring is oxidized very rapidly to both 1 and 4 hydroxy midazolam. Both these products are conjugated to glucuronides and are excreted in the urine. The metabolites have less than 1% activity of the parent drug.

MECHANISM AND SITE OF ACTION:

An important inhibitory neurotransmitter in the brain is gamma amino butric acid (GABA), while glycine is the major inhibitory neurotransmitter in the spinal cord and brainstem. The benzodiazepines augment GABA thus producing sedation and anticonvulsant activity, while anxiolysis and muscle relaxation appear to be due to glycine mimetic effects in the spinal cord and brainstem.

Among the benzodiazepines midazolam has the greatest affinity for the receptors, but dissociate faster from the receptor, thus accounting for the rapid onset and shorter duration of action. Given intrathecally or epidurally, midazolam produces analgesia which is

GABA mediated. Muscle relaxation produced by midazolam is due to potentiation of glycine action on the anterior horn cells.

PHARMACODYNAMICS:

CENTRAL NERVOUS SYSTEM:

Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and anterograde amnestic properties. It decreases the cerebral metabolic rate and cerebral blood flow. Cerebral perfusion pressure decrease as the systemic pressure falls more than the intracranial pressure. Given in doses of 0.25mg/kg it does not alter intracranial tension and therefore it can be used for neurosurgical procedures. Emergence from induction is more rapid than, diazepam, but not so, when compared with thiopentone. Midazolam decreases the anaesthetic requirement of inhalational agents.

CARDIOVASCULAR SYSTEM:

Midazolam decreases the myocardial contractility and systemic vascular resistance and causes vasodilatation, thus causing fall in arterial pressure. The fall in blood pressure is similar to that caused by hypnotic doses of thiopentone, greater than that caused by equipotent does of diazepam and less than that caused by propofol. It increases the heart rate. Midazolam does not abolish the stress

response to intubation, but the increase in heart rate and blood pressure are less than with diazepam. Midazolam does not alter coronary vascular resistance and does not cause coronary steal phenomenon.

RESPIRATORY SYSTEM:

Midazolam causes dose dependent depression of ventilation. In doses used for premedication or sedation,it does not alter the carbondioxide response, but in doses above 0.2mg/kg it causes respiratory depression. Apnoea produced by midazolam is dose related and is more common in patients premedicated with opioids, in chronic obstructive pulmonary disorder patients and following faster injection of the drug. Their respiratory depression is reversed by flumazenil.

INTRATHECAL MIDAZOLAM:

It is an agonist at the benzodiazepine binding site on a subunit of the pentameric $GABA_A$ receptor. This receptor is a chloride-inophore that, when activated typically stabilizes the transmembrane potential at or near the resting potential. In neurons this typically serve to decrease the excitability. In primary afferent terminals, a modest depolarization is observed that serves paradoxically, to

reduce the transmitter release, a form of presynaptic inhibition. Consistent with these effects and benzodiazepine subunit expression in dorsal root ganglia and on spinal neurons, benzodiazepine tends to suppress afferent evoked excitation in the substantia gelatinosa and motor horn.

DRUG INTERACTIONS:

Erythromycin, clarithromycin and fluconazole increase the effect of midazolam due to inhibition of cytochrome P450 III A enzyme. H2 receptor antagonist also inhibit cytochrome P450 III A enzyme. Aspirin and probenecid increase the effect by competing for protein binding site. Phenytoin, rifampicin and xanthines decrease the efficacy of midazolam due to increased metabolism by inducing cyto chrome P450.

SIDE EFFECTS:

Nausea and vomiting are minimal. Incidence of hiccough is 5.6%, cough is 1.5%.

REVIEW OF LITERATURE

1. Bion used ketamine 50 mg as a sole anaesthetic agent in spinal anaethesia and observed that its use was associated with 58 mm of surgical analgesia. Anaesthesia 1984 ; 39.
2. Kathirvel and colleagues were the first to use ketamine with local anaesthetics (bupivacaine) intrathecally and showed that the combination does not prolong the duration of post operative analgesia. Anaesthesia 2000 : 55.
3. Borbjerg and Colleagues used preservative free ketamine 5 mg intrathecally in rabbits for 14 consecutive days and concluded that even repeated injections lacked any neurotoxic effect. Anaesthesia Analgesia 2003 : 96,
4. Brion and Hawksworth and colleagues observed psychomimetic manifestations in 50% and 30% of their patients while using intrathecal ketamine in doses of 50 mg and 0.75 – 0.9mg/kg respectively. Regional Anaesthesia 1992 : 69
5. Togal and colleagues used ketamine in low doses (0.1mg/kg) and did not come across any side effects. This was done for prostate surgery in elderly patients. European Journal of anesthesia 2004 : 21.

6. Bharti and colleagues had found that post operative pain scores were lower in patients who received intrathecal midazolam (1mg) along with bupivacaine. Acta Anaesthesiology Scandinava 2003 : 47.

7. Kim and colleagues used intrathecal midazolam in doses of 1 and 2 mg along with bupivacaine and found that the duration of post operative analgesia was significantly prolonged and was dose dependent. British Journal of Anaesthesia 2001 : 86.

8. Tucker and colleagues in a cohort study, evaluated 574 patients who received intrathecal midazolam and then observed them for one month for a wide range of symptoms related to neurotoxicity. They concluded that administration of intrathecal midazolam upto 2 mg did not increase the occurrence of neurological symptoms. Anaesthesia Analgesia 2003 : 96

9. Addition of intrathecal midazolam to bupivacaine produces better post operative analgesia without prolonging recovery. The study was done in PG1 chandigarh for knee asthroscopy surgeries.

10. Prakash and colleagues from Vardhman Mahavir Medical College, New Delhi, used 2 doses of midazolam 1mg and 2 mg

with Bupivacaine intrathecally for patients undergoing caesarean section. The mean duration of post operative analgesia was 6.1 hours in 2 mg midazolam group, 4.3 hours in 1 mg midazolam group and 3.8 hrs with plain bupivacaine group.

11. The analgesic and sedative effects of intrathecal midazolam in perianal surgeries was reported in European Journal of anaesthesiology, Aug 2004.
12. Intrathecal midazolam combined with low dose bupivacaine improves postoperative recovery in diabetes patients undergoing foot debridment. This is reported in Acta Anaesthesiology Dec.2007.
13. Intrathecal midazolam in combination with intrathecal fentanyl for labor pain is published in Anaesthesia Analgesia, June 2004.
14. Improvement in postoperative pain relief with the addition of midazolam to an intrathecal injection of buprenorphine and bupivacaine. This is published in European Journal of Anaesthesiology, Nov 2003.

15. Midazolam can potentiate the analgesic effect of intrathecal bupivacaine on thermal or inflammatory induced pain. This is reported in Anaesthesia Analgesic, May 2003.

16. Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves post operative analgesia in orthopaedic surgery. This study was done by T. Murali Krishna and colleagues from PG1, Chandigarh and published in European Journal of Anesthesiology 2008 ; 25 ; 299-306.

17. Yang CY,WongCS, ChangTY, Host. Intrathecal Ketamine reduces morphine requirements in patients with terminal cancer pain.Miller 6th edition.

MATERIALS AND METHODS

- Approval from the Ethical Committee was obtained
- Written informed consent was taken from all patients
- Patients with physical status ASA I and ASA II were included in this prospective double blind study.
- Infra umbilical surgeries like herniorrhaphy, varicose vein surgery, orthopaedic surgeries with less than 3 hr duration were taken up for the study.
- Morbidly obese patients, pregnant women, patient with neurological disease or any contraindication for regional technique were excluded from the study.

Three groups were selected. Patients were randomly assigned to one of the three groups. Patients and anaesthesiologist were blinded to the test drug. The volume of the test drug was kept 3.5 ml in all patients.

After attaching the patients to monitors, baseline values of heart rate, systolic, diastolic, mean arterial pressure and oxygen saturation were noted. They were preloaded with 10ml/kg intravenous crystalloid solution.

PROCEDURE :

Under strict aseptic precaution, lumbar puncture was performed at L3-L4 interspace using a 25-G Quincke's needle.

After achieving free flow of cerebrospinal fluid the study drug was injected into the subarachnoid space.

Study Groups :

Each study group consisted of 30 patients. Patients in all 3 groups received 3 ml of bupivacaine (heavy) 0.5%. In addition, patients in group B received preservative free ketamine 0.1 mg/kg and those in group C received preservative free ketamine 0.1mg/kg and midazolam 0.02 mg/kg intrathecally. The exact amount of ketamine and midazolam were measured using a tuberculin syringe and the final volume of the test drug in all the groups was made up to 3.5 ml by adding normal saline.

PARAMETERS :

Heart rate, non invasive blood pressure and SPO2 were measured at 2.5 min interval of the drug injection for the first 20 min and thereafter every 10 min until the end of the surgery. Any decrease in MAP below 20% of the baseline or systolic pressure less than 90mmHg was treated with a bolus dose of ephedrine (6 mg).

SENSORY BLOCKADE:

Sensory blockade was assessed by pin prick in the mid axillary line at 1 min intervals until the level of block reached T10. The maximum height of the sensory blockade was noted at 20 min.

Onset of sensory block was defined as the time taken from injection of drug to sensory block at T10 and offset of sensory block was assumed when pinprick sensation at the S2 dermatome has returned. Duration of sensory block was defined as the time interval between onset of sensory block at T10 to regression of sensory block to S2.

MOTOR BLOCKADE :

Motor block was assessed by the Modified Bromage score.

0 - No motor loss

1 - Inability to flex hip

2 - Inability to flex knee joint

3 - Inability to flex ankle

This was assessed at 1 min interval until complete motor blockade occurred. Onset of motor block was defined as the time taken from injection of drug to development of complete motor block. (Bromage Score-3). Bromage score '0' was considered as

complete recovery from motor block. Duration of motor block was defined as time taken from onset of complete motor block to complete recovery of motor block.

PAIN :

Pain was assessed by an 11 point verbal rating scale (Score 0 – 10) which was explained to the patient preoperatively. If any patient complained of pain at any time in the intraoperative period, he / she was given general anaesthesia and was excluded from the study.

Post operatively pain was assessed at 2 hour interval for the first 12 hours and then at 4 hour interval for 24 hours. Rescue analgesia in the form of Inj. Tramadol 100 mg IM was given if the pain score was equal to or more than 4. Duration of pain free period was measured from the time of spinal administration of the drug to the time when the patient needed the first rescue analgesia drug. The total number of doses of rescue analgesic requirement in 24 hr was also noted.

SEDATION :

The level of sedation of the patients was assessed by the Ramsay sedation score.

1 - Anxious and agitated

2 - Co-operative

3 - Asleep but brisk response to loud voice

4 - Asleep with sluggish response to loud voice

5 - No response to loud voice

6 - No response to pain

It was assessed every 15 min after injecting the drug until the sedation score was 2. All patients were followed after surgery upto 24 hrs for any behavioural side effects, confusion, dizziness, nystagmus, nausea, vomiting or any neurological complications like numbness or pain in the opposite leg, incontinence or retention of bowel or bladder or genital dysaesthesias.

The main end points of our study were

1. Postoperative pain free interval
2. Haemodynamic stability shown in terms of requirement of ephedrine to treat hypotension.
3. Any neurological complication in 24 hrs.

Statistical Tools :

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2008).**

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATION AND RESULTS

In this randomized double blind study conducted in 90 patients, the subjects were allocated in to three groups.

Group A - Inj. 0.5% Bupivacaine 3ml + 0.5cc Normal saline

Group B - Inj. 0.5% Bupivacaine 3ml + 0.1mg/kg ketamine + upto 3.5 ml with normal saline

Group C - Inj.0.5%Bupivacaine 3ml +0.1mg/kg ketamine +0.02mg/kg of midazolam + upto 3.5 ml with normal saline

DEMOGRAPHIC DATA:

All 3 groups were comparable in age, height, weight, duration of surgery.

Table 1 : Age distribution

Age Group	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Upto 30 yrs	7	23.3	2	6.7	4	13.3
31-40	16	53.3	20	66.7	6	20
41-50	5	16.7	7	23.3	10	33.3
>50	2	6.7	1	3.3	10	33.3
Total	30	100	30	100	30	100
Range	26-63 yrs		28-60 yrs		23-61 yrs	
Mean	37.93		38.77		41.67	
SD	8.87		6.94		10.6	
'P' value for						
A.B & C	0.1433 Not Significant					
A & B	0.5042 Not Significant					
A & C	0.0721 Not Significant					
B& C	0.1425 Not Significant					

In all the three groups the mean age were comparable and they are not statistically significant.

Table 2: Sex distribution

Sex distribution	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Male	24	80	21	70	25	83.5
Female	16	20	9	30	5	16.5
Total	30	100	30	100	30	100
'P' value for A & B A & C B& C	0.556 Not Significant 0.7408 Not Significant 0.3598 Not Significant					

In all the three groups the sex distribution were comparable and they are not statistically significant.

Table 3 : Weight

Weight	Group A	Group B	Group C
Range	48-75	45-72	50-76
Mean	59.4	62.7	62.9
SD	7.8	6.7	7.4
'P' value for			
A.B. &C	0.1 Not Significant		
A & B	0.056 Not Significant		
A & C	0.0726 Not Significant		
B& C	0.9823 Not Significant		

In all the three the mean weight were comparable and they are not statistically significant.

TABLE - 4 : ASA PHYSICAL STATUS

ASA	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
I	23	76.7	25	83.3	25	83.3
II	7	23.3	5	16.7	5	16
'P' value for A & B A & C B& C	0.7469 Not Significant 0.7469 Not Significant 0.1.0 Not Significant					

The ASA physical status in all the three groups were comparable and they are not statistically significant.

Table - 5 : Onset of Sensory Block (minutes)

Onset of Sensory Block	Group A	Group B	Group C
Range	4.5-6.5	3.5-10	3-5
Mean	5.55	7.2	3.92
SD	0.54	2.04	0.5
'P' value for			
A.B. &C	0.0001 Significant		
A & B	0.0033 Significant		
A & C	0.0001 Significant		
B& C	0.0001 Significant		

In group A the mean onset of sensory block is 5.55 minutes

In group B the mean onset of sensory block is 7.2 minutes

In group C the mean onset of sensory block is 3.92 minutes

With addition of midazolam and ketamine the mean onset of sensory block is quicker compared to other two groups.

Table - 6 : Onset of Motor Block (minutes)

Onset of Motor Block	Group A	Group B	Group C
Range	7.5-10	7.5-10	5.5-7.5
Mean	8.55	8.55	6.78
SD	0.63	0.63	0.6
'P' value for			
A.B. &C	0.0001 Significant		
A & B	1.0 Significant		
A & C	0.0001 Significant		
B& C	0.0001 Significant		

In group A the mean onset of motor block is 8.55 minutes

In group B the mean onset of motor block is 8.55 minutes

In group C the mean onset of motor block is 6.78 minutes

With addition of midazolam and ketamine the mean onset of motor block is quicker compared to other two groups.

Table - 7 : Maximum Sensory Level

Maximum Sensory Level	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
T2	-	-	-	-	3	10
T4	4	13.3	4	13.3	21	70
T6	16	53.3	16	53.3	6	20
T8	10	33.3	10	33.3	-	-

Maximum sensory level of T4 was reached in 13.3% of cases in Group A

Maximum sensory level of T4 was reached in 13.3% cases in Group B

Maximum sensory level of T4 was reached in 70% of cases in Group C

With addition of Midazolam and ketamine the maximum sensory level and reached in higher compared to other two groups.

Table - 8 : Duration of Sensory Block

Duration of Sensory Block	Group A	Group B	Group C
Range	160-240	180-280	200-360
Mean	199.7	207	266.3
SD	17.3	21.4	41.6
'P' value for			
A.B. &C	0.0001 Significant		
A & B	1.2436 Not Significant		
A & C	0.0001 Significant		
B& C	0.0001 Significant		

In group A the mean duration of sensory block was 199.7 minutes

In group B the mean duration of sensory block was 207 minutes

In group C the mean duration of sensory block was 266.3 minutes

With addition of ketamine and midazolam the duration of sensory block is prolonged compared to other two groups.

Table - 9 : Duration of Motor Block

Duration of Motor Block	Group A	Group B	Group C
Range	100-180	150-240	160-240
Mean	159.7	181.3	208.7
SD	15.6	20.1	22.7
'P' value for			
A.B. &C	0.0001 Significant		
A & B	0.0001 Significant		
A & C	0.0001 Significant		
B& C	0.0001 Significant		

In group A, the mean duration of motor block is 159.7 minutes

In group B, the mean duration of motor block is 181.3 minutes

In group C, the mean duration of motor block is 208.7 minutes

With addition of ketamine and Midazolam the mean duration of motor block is prolonged compared to other two groups.

Table - 10 : Duration of pain free Interval (in Minutes)

Duration of Pain free Interval	Group A	Group B	Group C
Range	240-440	200-360	360-900
Mean	303	296	473
SD	57.4	32.5	136.2
'P' value for			
A.B. &C	0.0001 Significant		
A & B	1.0002 Significant		
A & C	0.0001 Significant		
B& C	0.0001 Significant		

In group A the mean duration of pain free interval is 303 minutes

In group B the mean duration of pain free interval is 296 minutes

In group C the mean duration of pain free interval is 473 minutes

With addition of ketamine and Midazolam the mean duration of pain free interval is prolonged compared to other two groups.

Table 11 : Number of rescue analgesics

No. of rescue analysis	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
1	-	-	13	43.3	30	100
2	19	63.3	17	56.7	-	-
3	11	36.7	-	-	-	-
Range	2-3		1-2		1	
Mean	2.37		1.57		1.0	
SD	0.49		0.5		-	
'P' value for						
A.B & C	0.0001 Significant					
A & B	0.0001 Significant					
A & C	0.0001 Significant					
B& C	0.0001 Significant					

In group A the number of rescue analgesics required were in a range of 2-3

In group B the number of rescue analgesics required were in a range of 1-2

In group C the number of rescue analgesics required were in a range of 1

With addition of ketamine and midazolam the number of rescue analgesics required are less compared to other two groups.

Table 12 : Systolic Blood Pressure

Systolic B.P.	Group A	Group B	Group C
Range	104-130	110-136	106-142
Mean	117.6	120.1	122.2
SD	7.7	5.2	10.1
'P' value for			
A.B. &C	0.1461 Not Significant		
A & B	0.2755 Not Significant		
A & C	0.0604Not Significant		
B& C	0.3082 Not Significant		

In all three groups the mean systolic blood pressure was comparable and they are not statistically significant.

Table - 13 : Minimum Systolic Blood pressure

Minimum Systolic B.P.	Group A	Group B	Group C
Range	84-110	88-120	80-110
Mean	95.4	104.7	94.9
SD	8.0	8.3	8.0
'P' value for			
A.B. &C	0.0001 Significant		
A & B	0.0002 Significant		
A & C	0.9402 Not Significant		
B& C	0.0001 Significant		

In group A the mean minimum systolic blood pressure is 95.4 mmHg

In group B the mean minimum systolic blood pressure is 104.7 mmHg

In group C the mean minimum systolic blood pressure is 94.9 mmHg

The minimum systolic blood pressure in group A is comparable to group C

The minimum systolic blood pressure in group B and C are not significant and this finding is an added advantage to ketamine midazolam group.

In group B the fall in systolic blood pressure is less comparable to other two groups.

TABLE 14 : Vasopressor

Vasopressor	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
Yes	16	53.3	4	13.3	14	46.7
No	14	46.7	26	86.7	16	53.3
'P' value for						
A & B	0.0026 Significant					
A & C	0.7963 Not Significant					
B& C	0.0112 Not Significant					

The vasopressors required in group A and C were compared and they are not statistically significant. In both these groups the vasopressor requirement was comparable.

In group B the vasopressor requirement is less compared to other two groups.

Table 15 : Sedation Score

Sedation Score	Group A		Group B		Group C	
	No.	%	No.	%	No.	%
1	5	16.7	-	-	-	-
2	25	83.3	8	26.7	7	23.3
3	-	-	22	73.3	23	76.7
Range	1-2		2-3		2-3	
Mean	1.83		2.73		2.77	
SD	0.38		0.45		0.43	
'P' value for						
A.B & C	0.0001 Significant					
A & B	0.0001 Significant					
A & C	0.0001 Significant					
B& C	0.7675 Not Significant					

In group A the range of sedation score was 1-2

In group B the range of sedation score was 2-3

In group C the range of sedation score was 2-3

In group B and group C the sedation score was higher compared to group A.

DISCUSSION

Ketamine and midazolam are two important anaesthetic drug which are administered in various routes. Ketamine as slow inrathecal agent was used by Bion and colleagues in 1984.Kathirvel and colleagues were the first to use ketamine with local anaesthetics intrathecally.

Spinal ketamine binds to the phencyclidine site of the NMDA receptor gated calcium channel and inhibits the NMDA receptors non competitively.Its direct axonal blocking effect produces some local anaesthetic activity.

Intrathecal midazolam has been shown to have analgesic properties and potentiates the effects of local anaesthetics. It is an agonist at the benzodiazepine site on a subunit of the pentomeric GABA a receptor. Midazolam tends to suppress afferent evoked excitation in the substantia gelatinosa and motor horn of the spinal cord.

Bharti and colleagues had found that postoperative pain Scores were lower in patients who received intrathecal midazolam with bupivacaine.

Kim and colleagues used intrathecal midazolam in doses of 1 and 2 mg along with bupivacaine and found that the duration of postoperative analgesia was significantly prolonged by addition of intrathecal midazolam and was dose dependent.

In this study addition of ketamine and midaolam to bupivacaine (Group C) prolongs the duration of sensory and motor blockade. The mean pain free period was also significantly prolonged. The number of reserve analgesics were comparatively less .This finding is consistent with the study done by T.Murali Krishna and colleagues who used low doses of ketamine and midazolam with bupivacaine for orthopaedic surgeries.

In this study addition of ketamine to bupivacaine (Group B) does not alter significantly the time for onset or duration of sensory and motor blockade.The duration of pain free period was also less compared to the midazolam. Ketamine group. This finding is consistent with the study done by T.Muralikrishna and colleagues. Kathirvel and colleagues showed that combination of ketamine with bupivacaine does not prolong postoperative analgesia.

This infers that midazolam in (dose 0.02 mg /kg) when added to ketamine in dose (0.1 mg/kg) and bupivacaine prolongs

significantly the duration of post operative analgesia. This might be due to synergistic action of intrathecal midazolam. Ketamine and bupivacaine.

In this study addition of low dose of ketamine with bupivacaine (group B) resulted in stable haemodynamics with decreased incidence of hypotension. This finding is consistent with the previous studies by T.Murali Krishna and colleagues, Kathirvel and colleagues and Bion and colleagues.This may be due to diffusion of ketamine into the venous system of spinal cord which in turn results in cardiovascular stimulation and hemodynamic stability after spinal anesthesia.

In this study the level of sedation was assessed by Ramsay sedation score. The level of sedation at 15 and 30 min after the block was higher in Group B and C compared to Group A . The maximum level of sedation observed is any patient was 3.No patient required any manoeuvre to maintain airway. Thus intrathecal midazolam and ketamine in low doses had minimal effect on the level of sedation. This finding is consistent with the observation made by T.Murali Krishna and colleagues

SUMMARY

This study is conducted in patients of ASA I and II undergoing elective infraumbilical surgeries.

3 groups with 30 cases each were selected. Group A received 0.5% bupivacaine 3 ml with 0.5ml normal saline.

Group B received 0.5% bupivacaine 3ml with 0.1 mg / kg ketamine and the volume made upto 3.5 ml with normal saline.

Group C received 0.5% bupivacaine 3 ml with 0.1mg/kg ketamine and 0.02mg/kg midazolam and the volume made upto 3.5ml with normal saline.

The post operative analgesia was significantly prolonged in group C with decreased requirement of rescue analgesics over a 24 hour period. There was haemodynamic stability in group 'B' which used ketamine along with bupivacaine whereas Group A and Group C required vasopressors. The duration of the post operative analgesia was not prolonged in group B.

CONCLUSION

From the study it was concluded that low doses of preservative free ketamine (0.1mg/kg) and midazolam (0.02mg/kg) when added to bupivacaine intrathecally provides prolonged post operative analgesia without any significant side effects.

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PROFORMA

NAME : HT :

AGE/SEX : WT:

DATE :

IP NO :

ASA :

DIAGNOSIS :

Group A : 0.5% Bupivacaine 3.0ml

Group B : 0.5% Bupivicaine 3.0ml+Inj. Ketamine 0.1 mg/kg

Group C : 0.5% Bupivicaine 3.0ml+Inj. Ketamine 0.1mg/kg+Inj Midazolam 0.02mg/kg

Premedication : inj. Atropine 0.6mg + Inj. Midazolam2 mg IM

SPINAL NEEDLE GAUGE: Interspace :

Time of SAB	Onset of sensory block (Time of injection to height at T10 level	Max. height of sensory block (at 20 min)	Onset of motor block (time of injection to complete motor block)	Time to reach 2 segment regression

SEDATION SCORE (RAMSAY)

S. No.		0 min	15 min	30 min	1 hr	1 ½ hr	2 hrs	2 ½ hrs	3 hrs
1.	Anxious and agitated								
2	Co-operative								
3.	Asleep but brisk response to loud voice								
4.	Asleep with sluggish response to loud voice								
5.	No response to loud voice								
6.	No response to pain								

HAEMODYNAMICS:

Time	HR	NIBP	SPO2	Vasopressor
Pre-op				
SAB				
5 min				
10 min				
15 min				
20 min				
30 min				
40 min				
50 min				
1 hr				
1 ½ hr				
2 hrs				
2 ½ hrs				
3 hrs				

DURATION OF SURGERY:

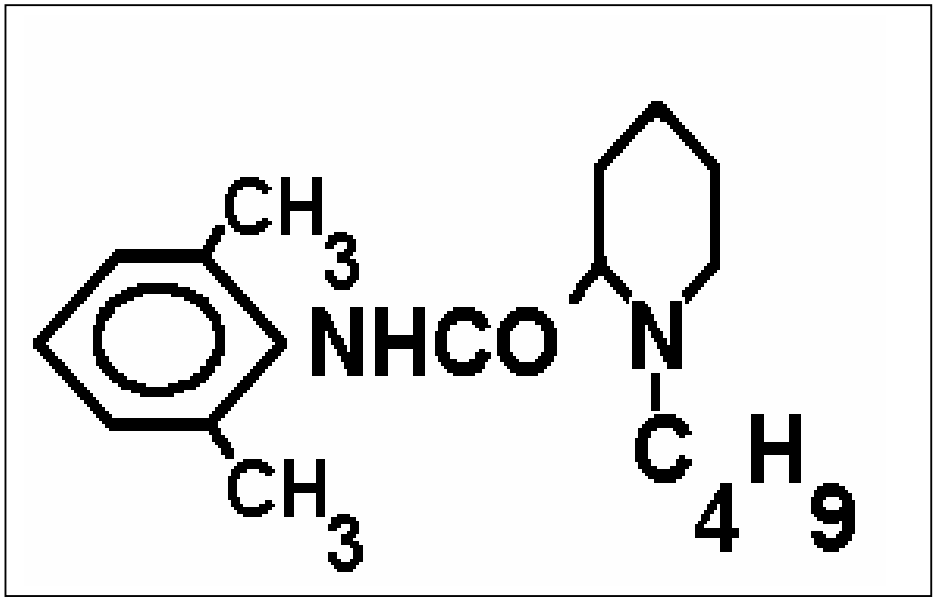
VRS 1-10									

MOTOR (MODIFIED BROMAGE SCALE):

Time									
0.No motor loss									
Inability to flex hip									
Inability to flex knee joint									
Inability to flex ankle									

OFFSET OF SENSORY BLOCK (PINPRICK SENSATION AT S2 DERMATOME HAS RETURNED)
OFFSET OF MOTOR BLOCK
(Complete recovery from motor block-score 0)
DURATION OF SENSORY BLOCK
DURATION OF MOTOR BLOCK
TIME OF RESCUE ANALGESIA
TIME TO VOID URINE
TIME OF PAIN FREE INTERVAL
MEDICATION – inj. ATROPINE 0.6 mg i.v. if PR 60/min
If systolic pressure <90mm Hg or below 20% of base line MAP Give inj. Ephedrine and rush IV fluids.

STRUCTURE OF BUPIVACAINE



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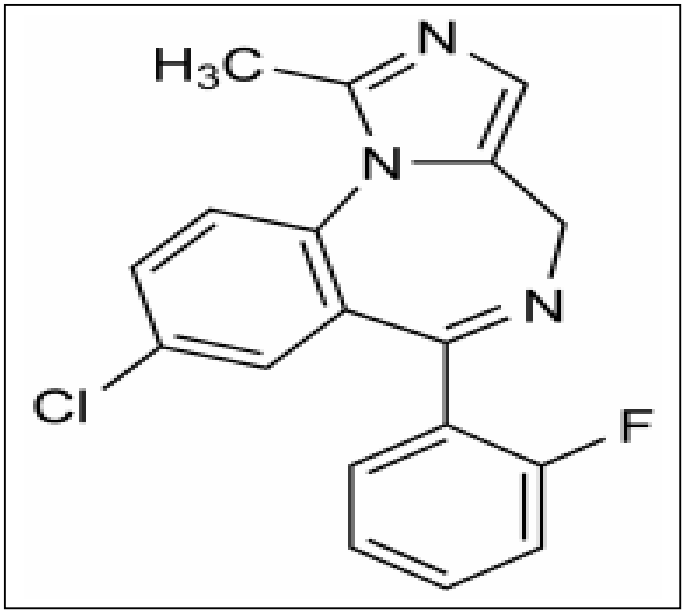
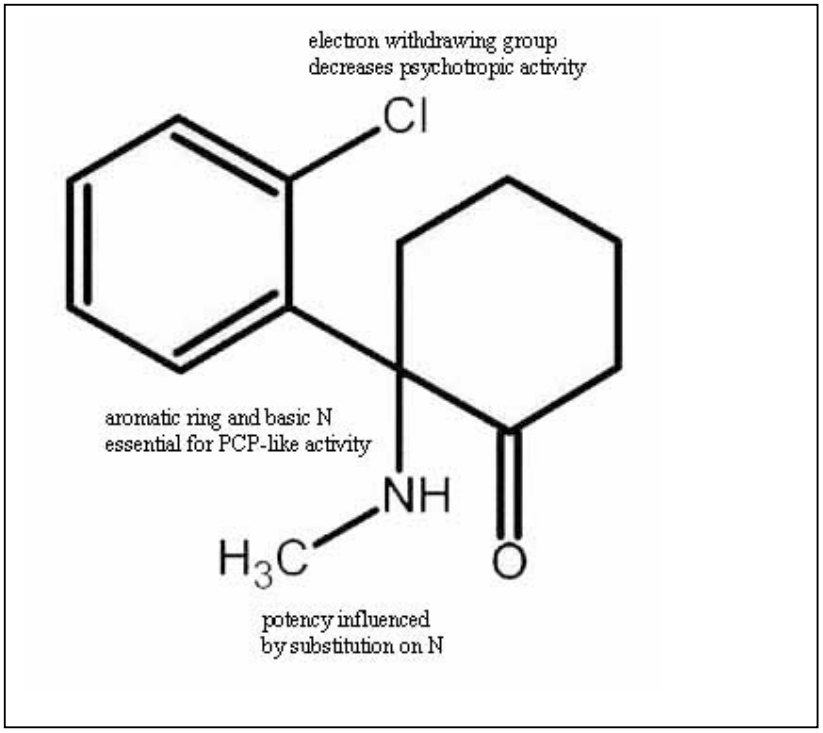
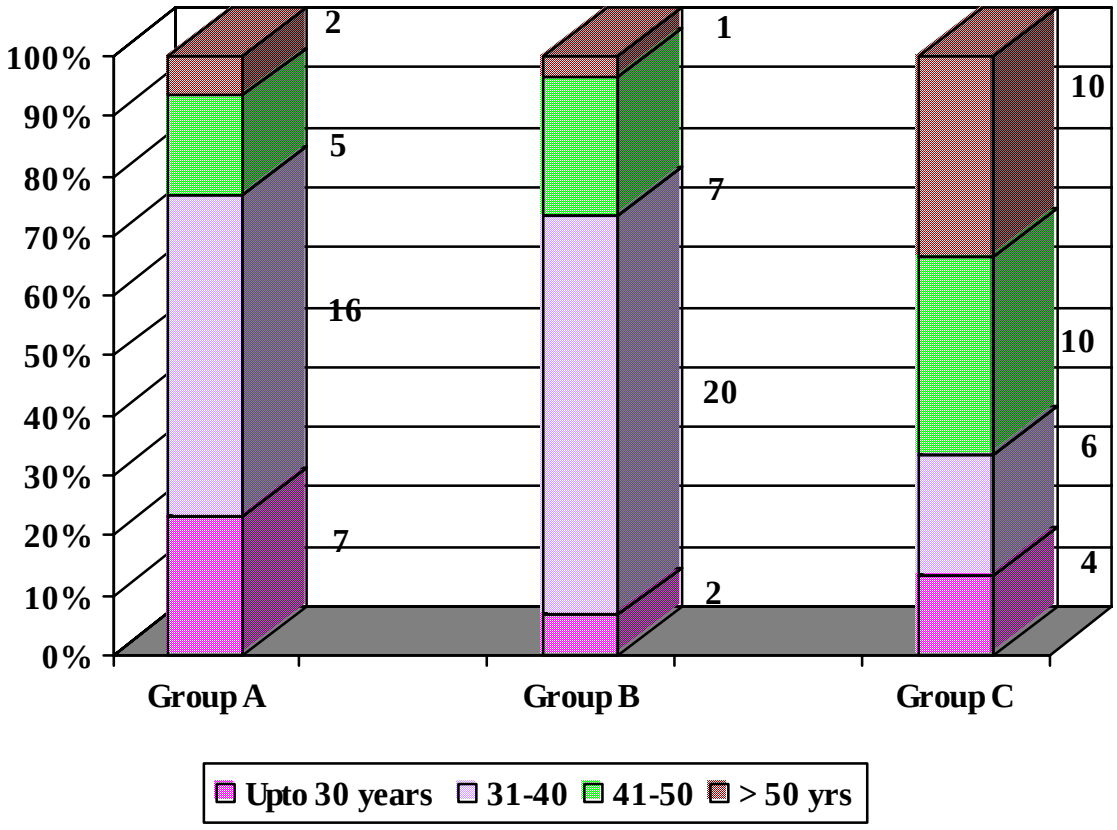


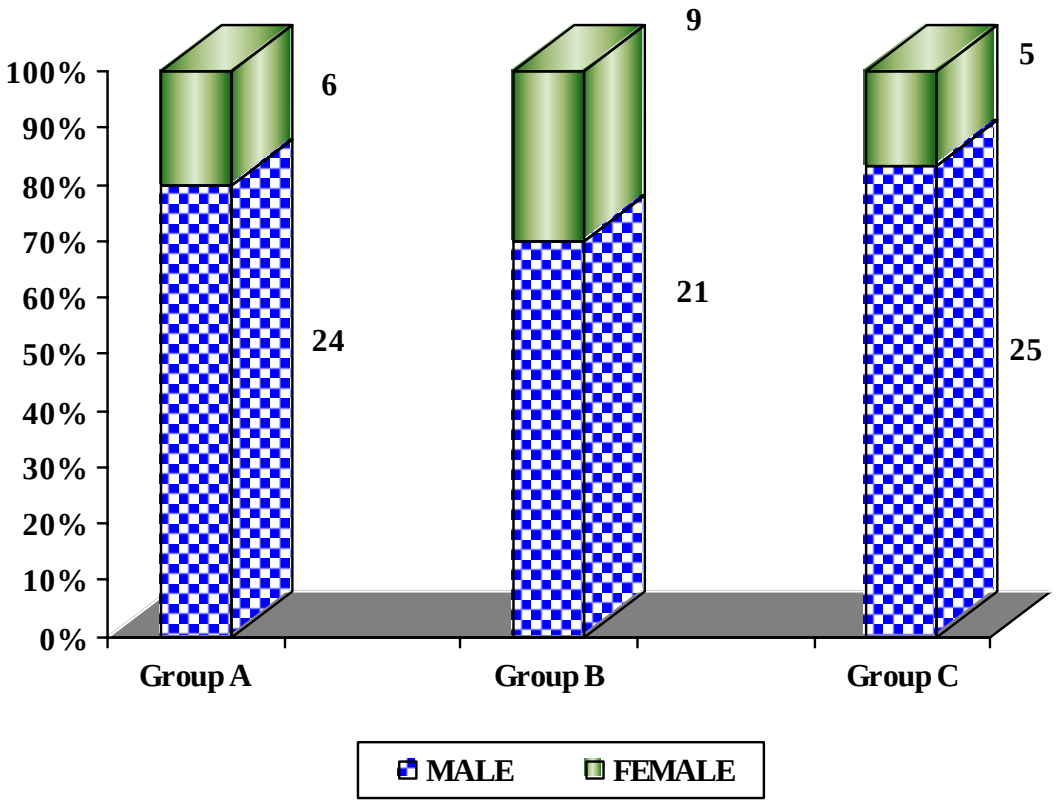
STRUCTURE OF KETAMINE



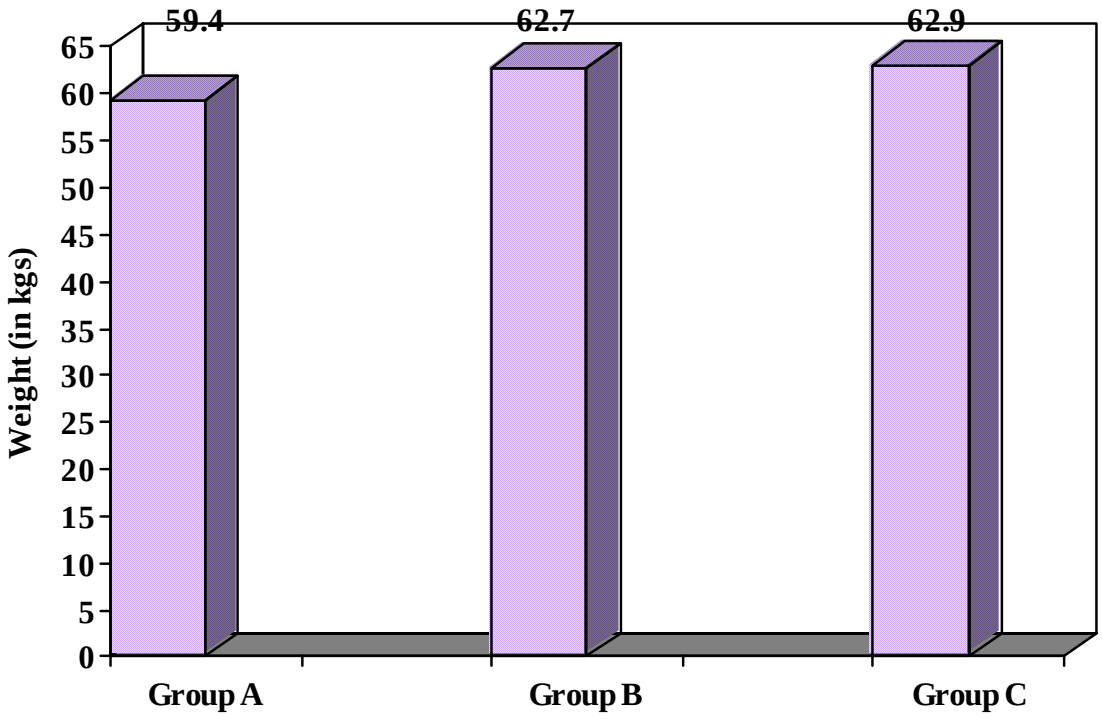
AGE DISTRIBUTION



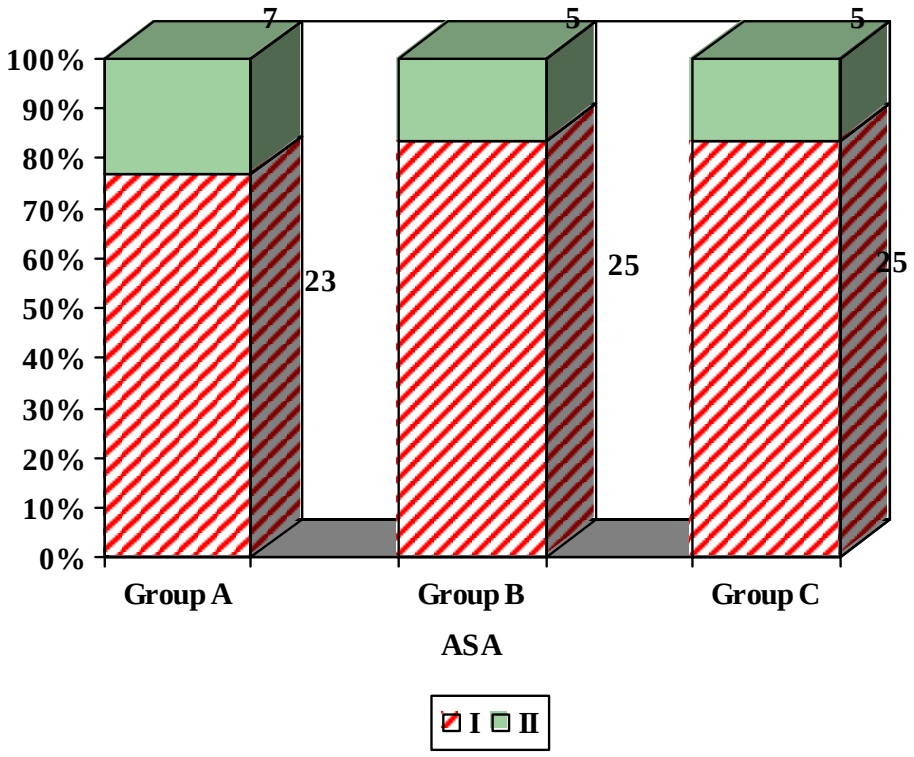
SEX DISTRIBUTION



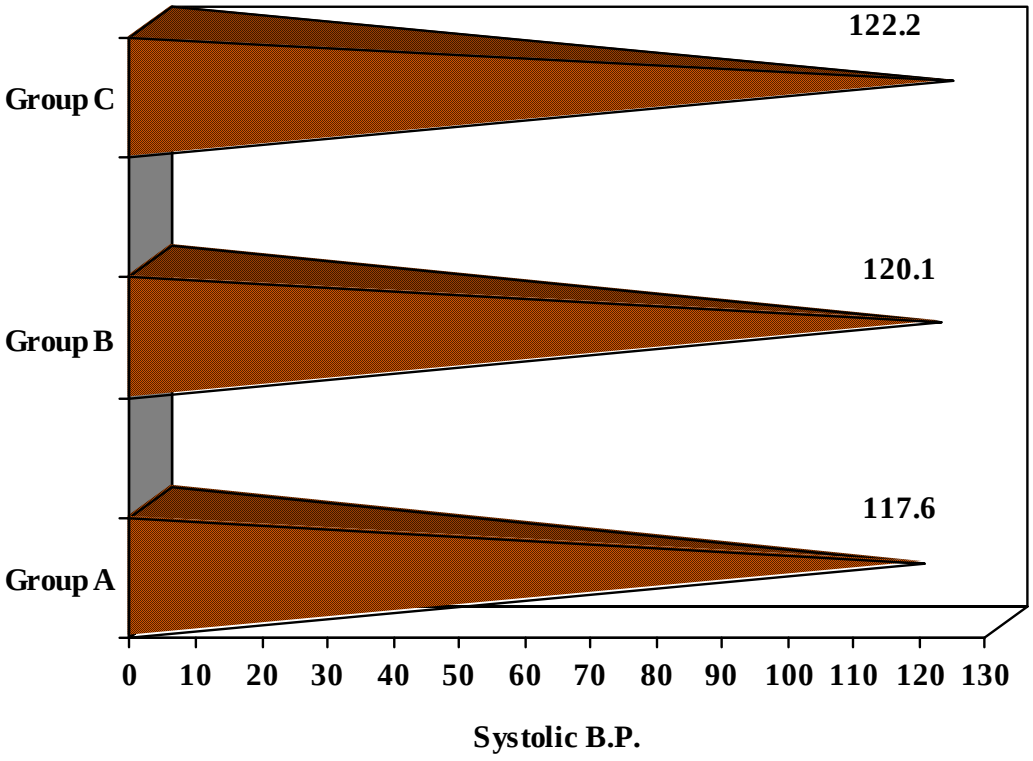
WEIGHT


59.4
62.7
62.9
65
60
55
50
45
40
35
30
25
20
15
10
5
0
Weight (in kgs)
Group A
Group B
Group C

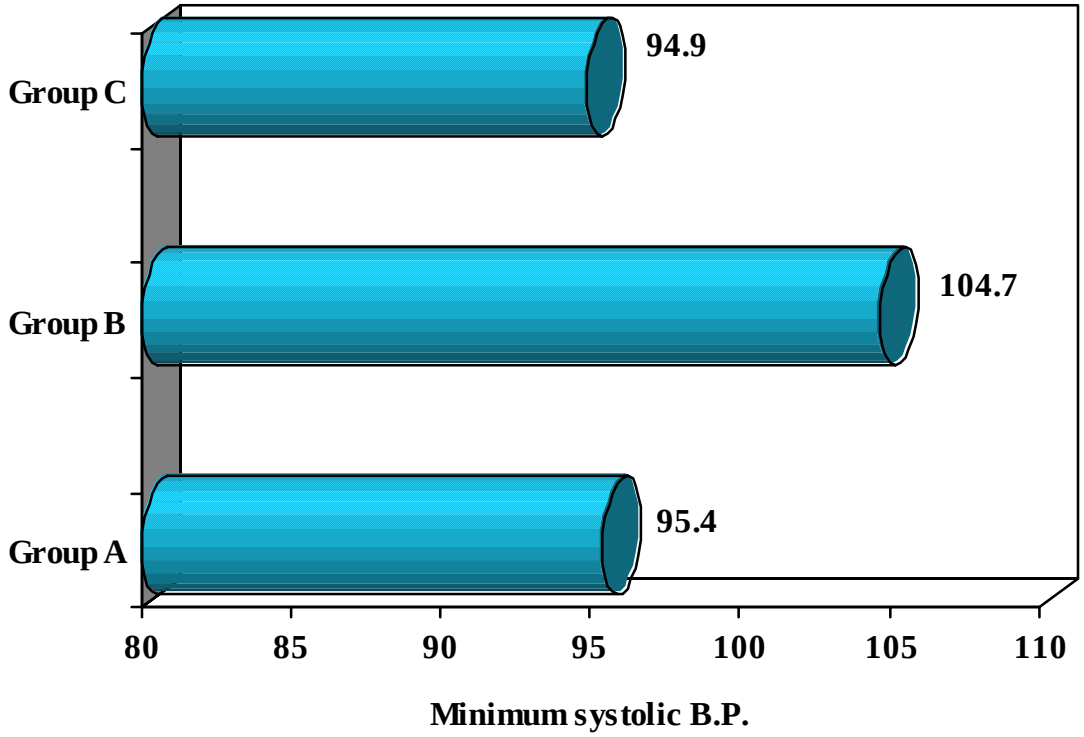
ASA


7
5
5
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
23
25
25
Group A
Group B
Group C
ASA
I
II

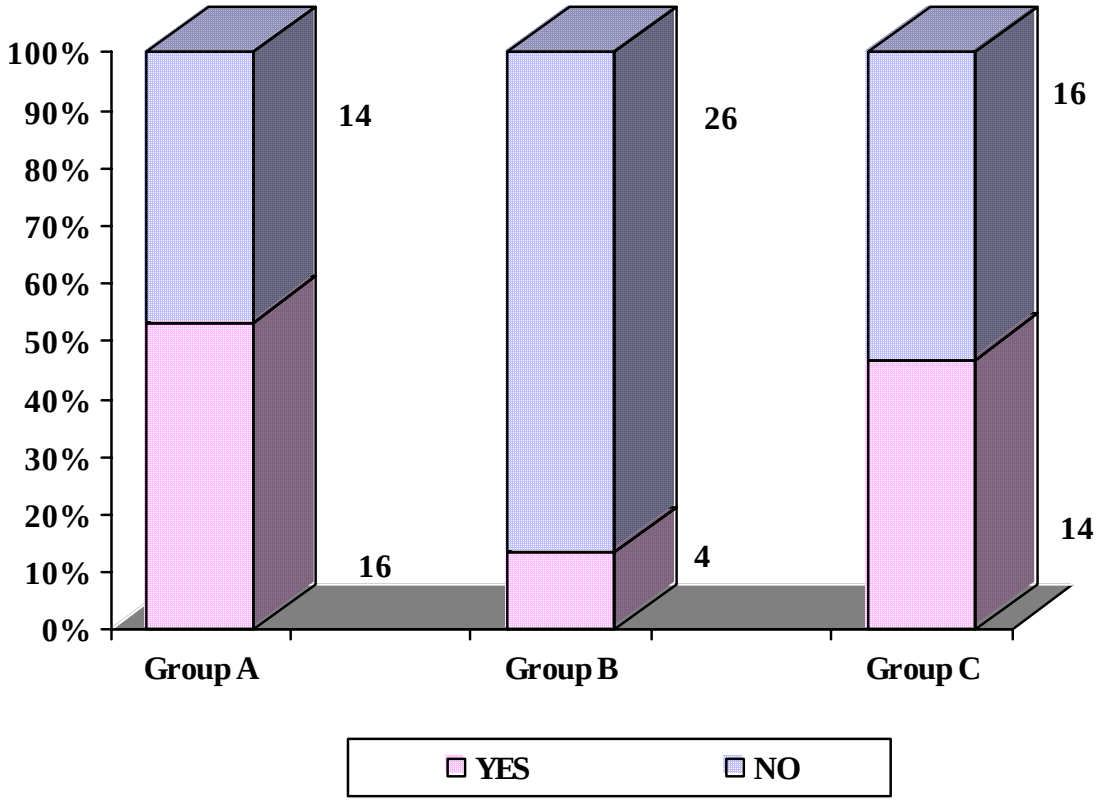
SYSTOLIC B.P.


122.2
Group C
120.1
Group B
117.6
Group A
0 10 20 30 40 50 60 70 80 90 100 110 120 130
Systolic B.P.

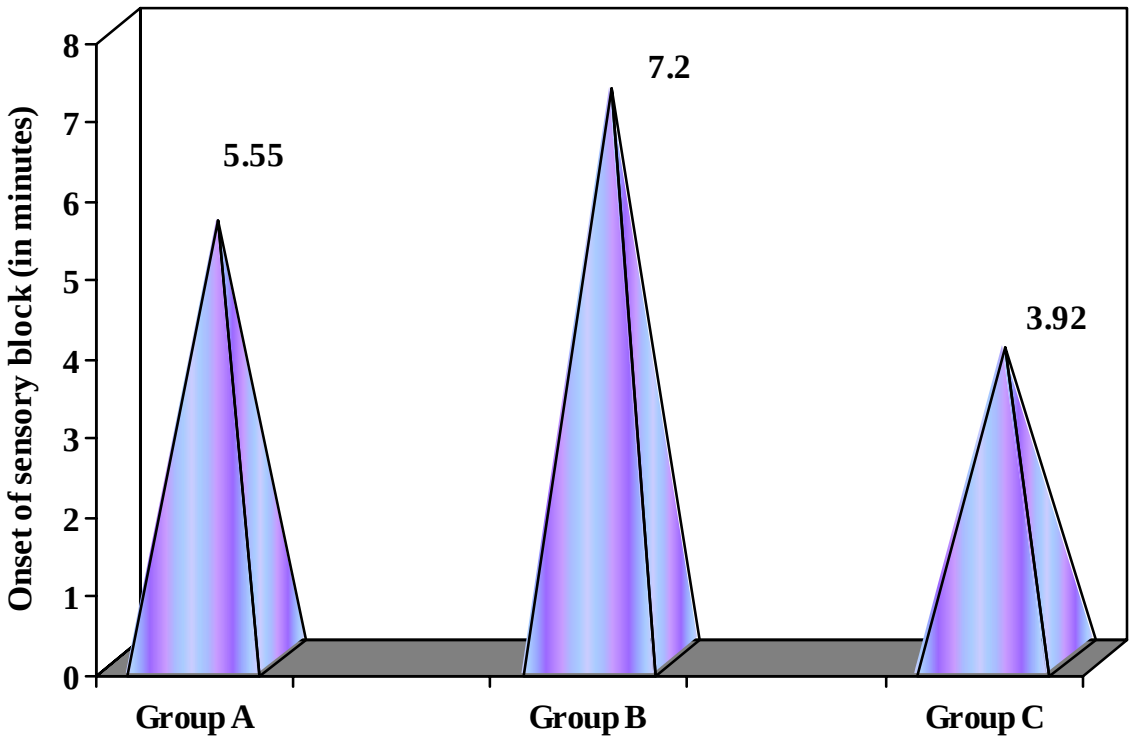
MINIMUM SYSTOLIC B.P.



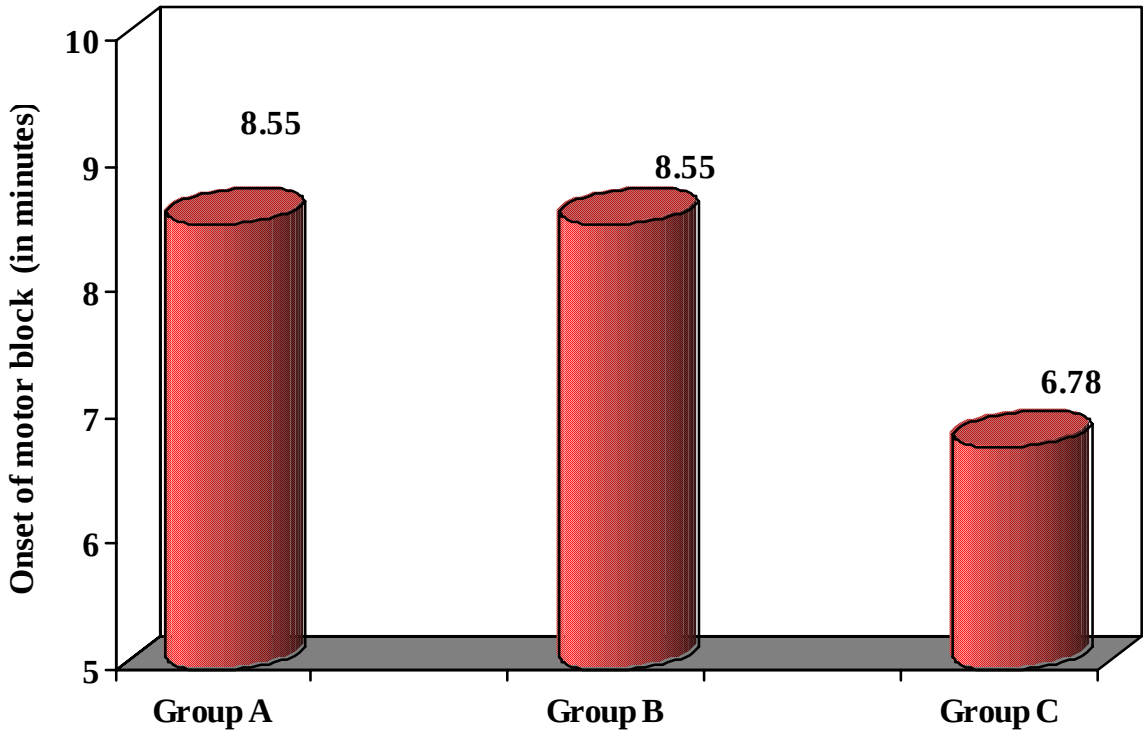
VASOPRESSOR



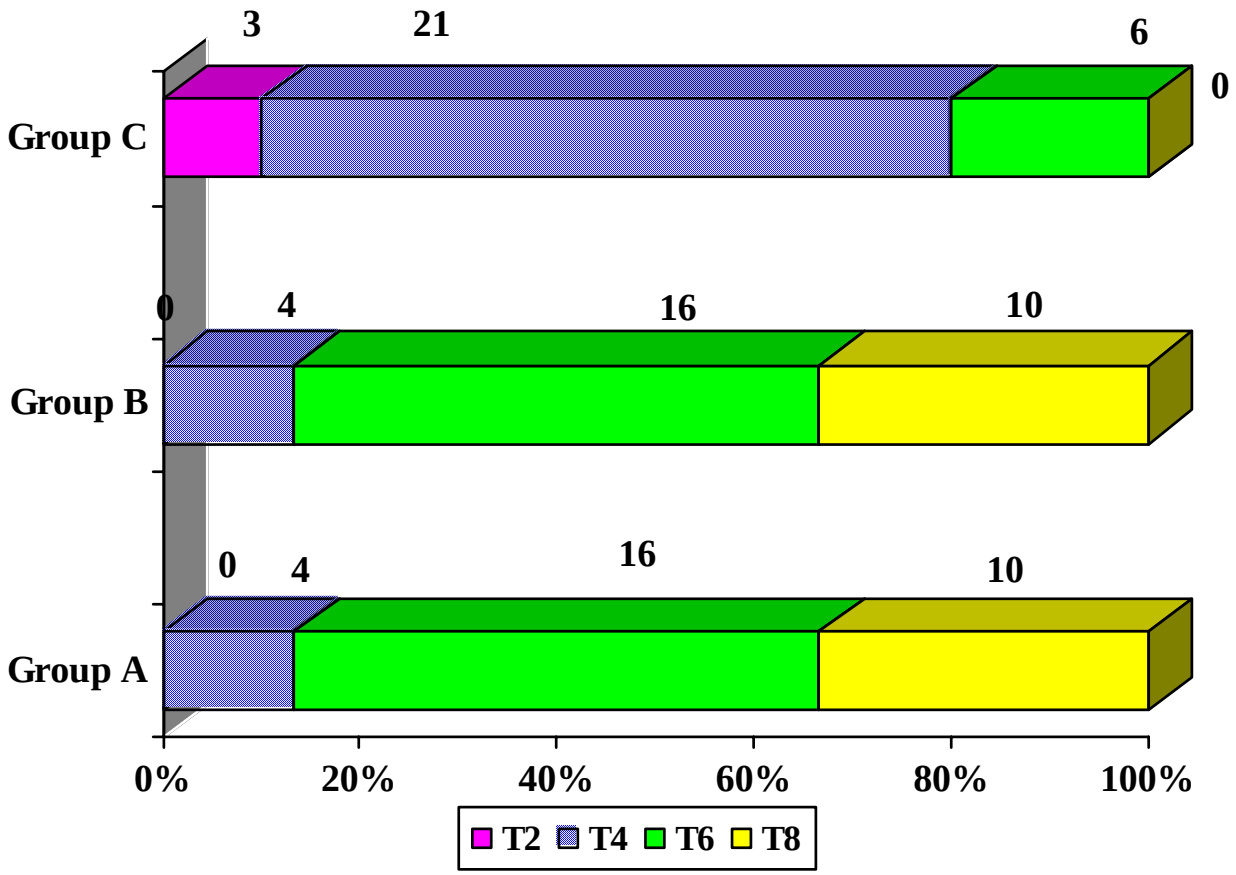
ONSET OF SENSORY BLOCK



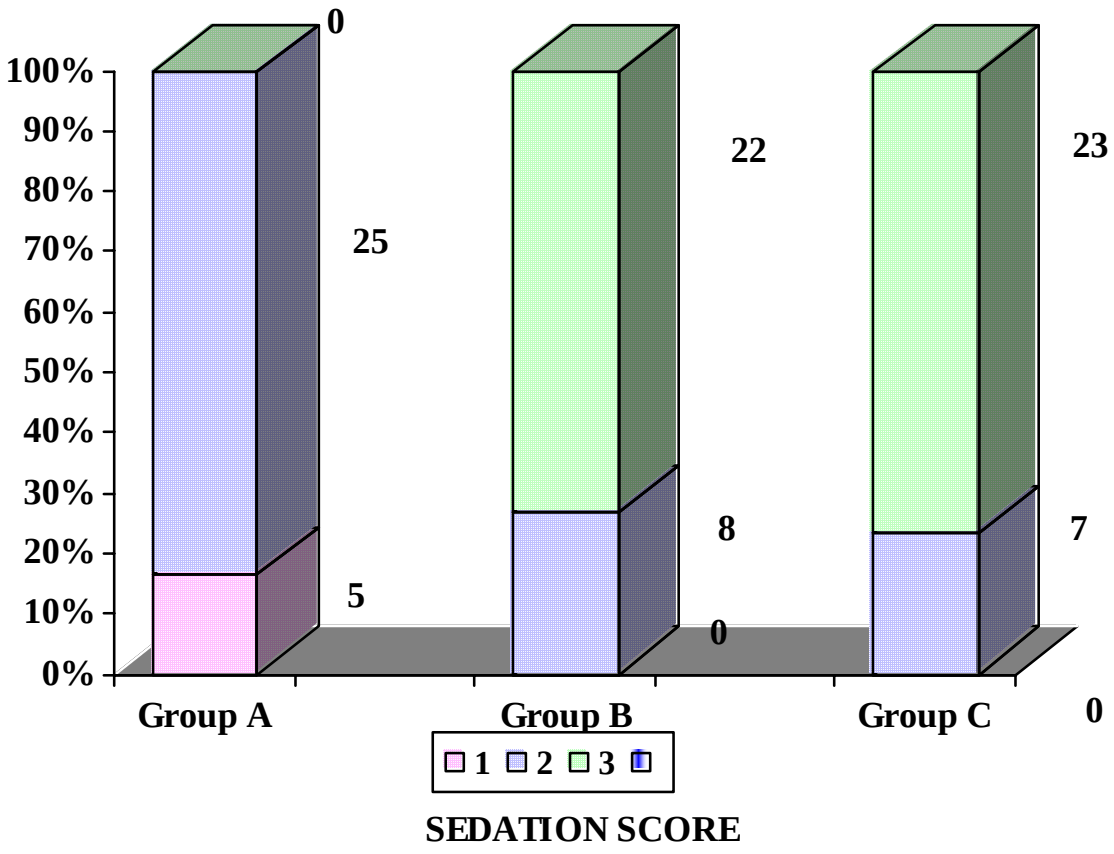
ONSET OF MOTOR BLOCK



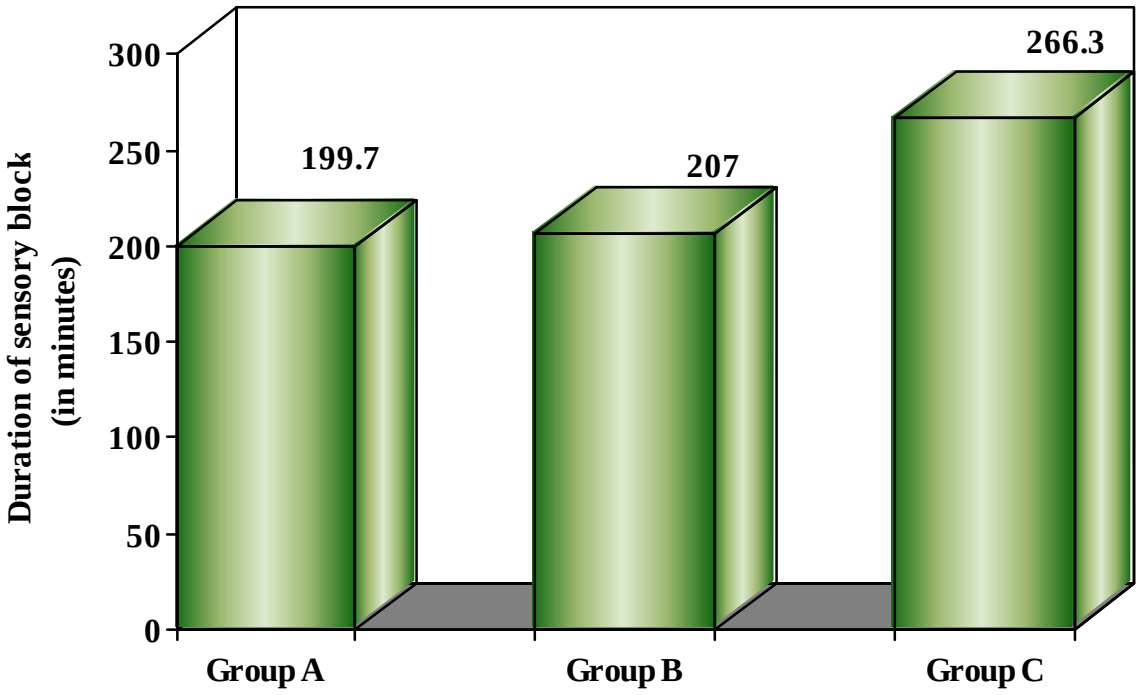
MAXIMUM SENSORY LEVEL



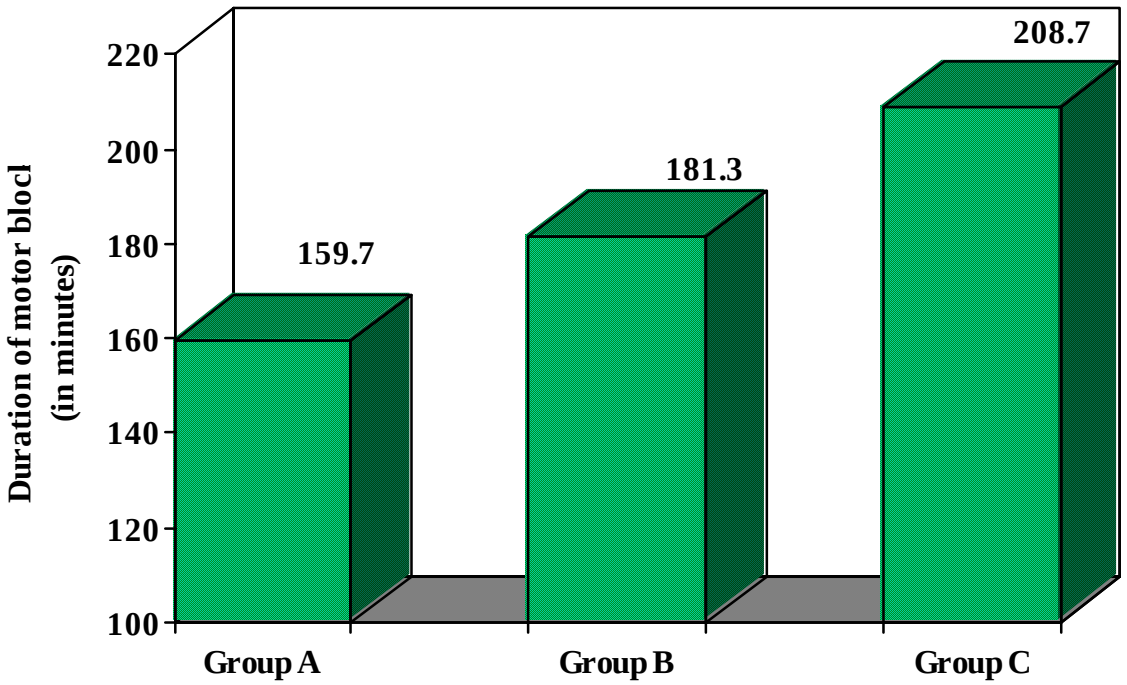
SEDATION SCORE



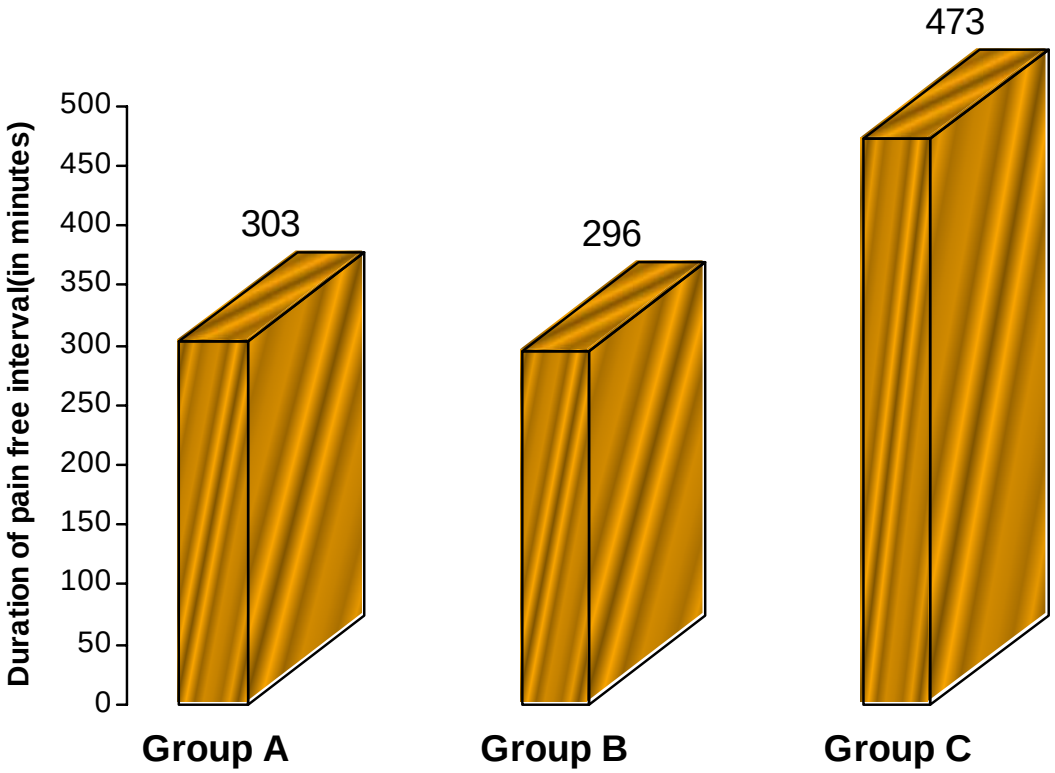
DURATION OF SENSORY BLOCK



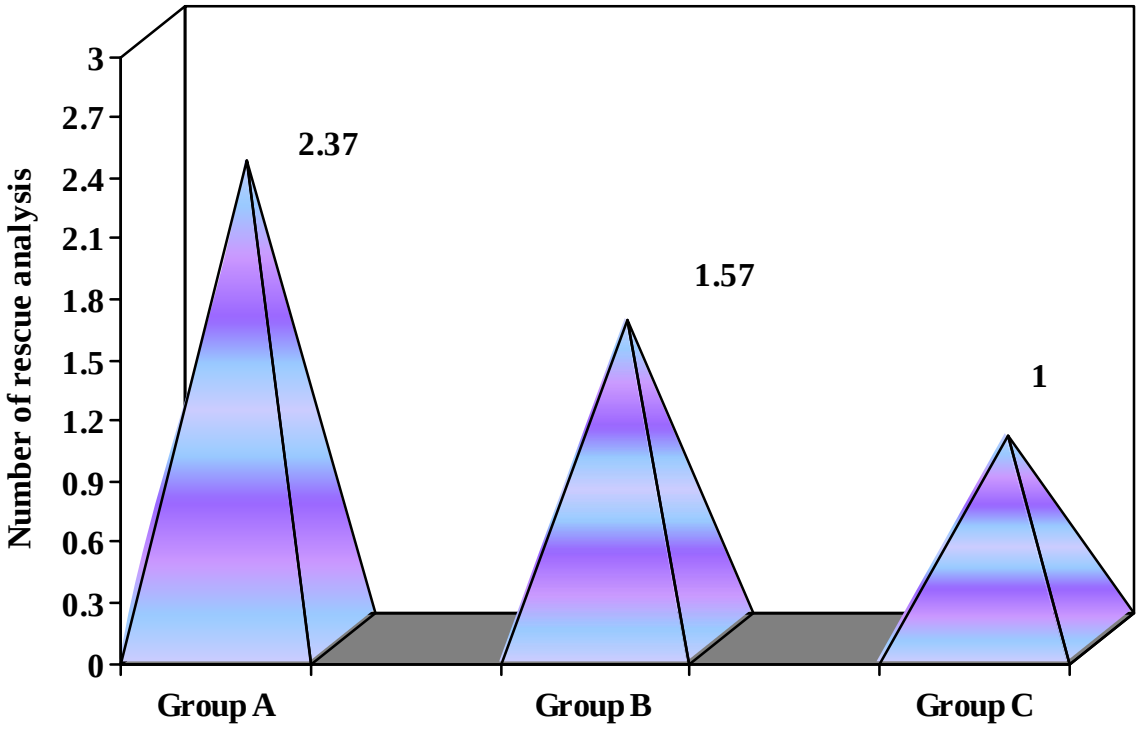
DURATION OF MOTOR BLOCK



DURATION OF PAIN FREE INTERVAL



NUMBER OF RESCUE ANALGESICS



S.NO	Group	Age	Sex	IP NO.	Ht	Wt	ASA	BP - S	BP-D	MIN BP-S	Vaso pressor	OSB	OMB	MSL	Sed Score	DSB	DMB	PFI	Rescue No.
1	A	35	F	50131	164	52	I	120	80	90	YES	5	8	T6	2	180	160	240	2
2	A	44	M	51291	160	48	I	116	74	98	NO	5.5	8.5	T8	2	200	150	300	2
3	A	38	M	6108	155	60	I	128	72	98	NO	5	8	T6	2	220	180	360	3
4	A	38	M	7432	165	55	II	116	70	104	NO	4.5	9	T8	2	210	160	300	3
5	A	40	M	50041	172	58	II	120	68	106	NO	5	8.5	T8	2	210	170	320	2
6	A	42	M	54931	168	54	I	118	74	110	NO	5.5	9	T6	2	180	180	300	3
7	A	36	F	49791	155	52	I	124	80	104	NO	6	10	T4	2	210	160	310	2
8	A	28	M	5164	170	56	I	120	78	110	NO	6.5	9	T8	2	210	170	320	3
9	A	26	M	53001	175	58	I	118	74	104	NO	5.5	8.5	T6	2	180	180	310	2
10	A	28	M	49821	170	62	I	124	78	106	NO	6	8.5	T8	2	200	180	300	3
11	A	30	F	5675	164	60	I	120	64	90	YES	5.5	8	T4	2	210	170	320	3
12	A	32	F	49381	160	65	I	104	70	86	YES	5	8	T6	2	180	160	300	2
13	A	34	M	51061	158	60	I	108	68	88	YES	4.5	8.5	T6	2	210	180	240	2
14	A	28	M	50032	170	65	I	110	70	84	YES	5	8	T6	2	200	150	280	2
15	A	30	M	41161	172	64	I	108	66	88	YES	5.5	8.5	T8	2	210	160	300	2
16	A	35	M	40113	160	50	I	120	70	90	YES	5	8	T8	2	180	160	480	2
17	A	30	F	45113	154	55	I	130	68	90	YES	5.5	7.5	T6	2	200	160	360	2
18	A	36	M	6013	170	60	I	126	80	90	YES	6	8.5	T6	2	220	160	480	2
19	A	35	F	4972	155	62	II	128	70	104	NO	5.8	8.8	T6	2	210	150	420	2
20	A	38	M	5610	165	70	I	129	74	90	YES	6	9.5	T8	1	180	160	420	2
21	A	32	M	64101	168	72	I	130	68	92	YES	6.5	8.6	T4	2	190	100	480	2
22	A	40	M	51612	170	75	II	120	70	90	YES	5.5	7.5	T6	1	200	150	360	2
23	A	48	M	43211	172	68	I	110	70	100	NO	5.8	8.8	T8	1	210	160	390	2
24	A	60	M	6408	168	74	I	106	74	102	NO	6	9.5	T4	2	220	140	420	2
25	A	63	M	41151	170	68	II	108	68	104	NO	6.5	8	T6	2	240	150	400	3
26	A	50	M	6009	164	49	I	110	70	90	YES	5.5	8.6	T6	1	200	170	380	2
27	A	48	M	43211	168	55	II	117	74	90	YES	5	8.8	T6	1	210	160	360	3
28	A	36	M	5631	170	48	I	118	68	88	YES	5.8	8.5	T8	2	180	160	540	3
29	A	38	M	6009	165	50	I	114	70	86	YES	6	8	T6	2	160	150	420	3
30	A	40	M	7104	168	56	II	108	68	90	NO	5.5	10	T6	2	180	150	480	3

S.NO	Group	Age	Sex	IP NO.	Ht	Wt	ASA	BP - S	BP-D	MIN BP-S	Vaso pressor	OSB	OMB	MSL	Sed Score	DSB	DMB	PFI	Rescue No.
31	B	50	M	40329	168	50	I	120	80	120	NO	4	8	T6	3	180	160	300	1
32	B	40	F	50321	156	56	I	124	78	108	NO	5	8.5	T8	2	200	150	240	2
33	B	35	M	40621	170	60	I	120	80	110	NO	3.5	8	T6	3	220	180	360	2
34	B	60	F	3990	165	62	II	120	74	114	NO	4	9	T8	3	210	160	300	1
35	B	45	M	4086	170	63	I	128	80	106	NO	5	8.5	T8	3	210	170	200	1
36	B	44	F	51002	156	70	I	126	80	98	NO	5	9	T6	3	180	180	360	2
37	B	35	M	3409	160	72	I	124	84	94	NO	4.5	10	T4	3	210	160	300	2
38	B	36	F	7186	149	58	I	120	80	96	NO	4	9	T8	2	210	170	300	1
39	B	40	M	4009	156	68	II	110	70	104	NO	3.8	8.5	T6	3	180	180	240	2
40	B	45	M	41321	154	70	I	116	70	110	NO	10	8.5	T8	3	200	180	270	2
41	B	38	M	51026	165	72	II	114	70	102	NO	9	8	T4	2	210	170	280	2
42	B	34	M	53029	172	68	I	116	72	104	NO	8.3	8	T6	3	180	160	320	2
43	B	42	F	54011	160	70	I	114	80	102	NO	8.5	8.5	T6	3	210	180	300	2
44	B	50	M	51102	163	68	I	118	78	100	NO	8	8	T6	3	200	150	340	2
45	B	49	M	5006	149	66	I	120	76	98	NO	9	8.5	T8	3	210	200	320	2
46	B	35	F	10064	165	45	I	120	80	98	NO	7.5	8	T8	2	180	200	300	2
47	B	40	M	2019	160	58	I	116	78	104	NO	8	7.5	T6	2	200	180	320	2
48	B	35	M	51132	172	60	I	118	80	110	NO	7.5	8.5	T6	3	220	200	300	2
49	B	40	M	50096	168	64	I	120	72	116	NO	8	8.8	T6	3	210	160	280	2
50	B	36	F	51121	169	68	I	124	78	120	NO	8.5	9.5	T8	3	180	180	280	2
51	B	35	M	5493	154	64	I	117	76	116	NO	9	8.6	T4	2	190	200	280	1
52	B	38	M	56001	155	62	I	118	78	104	NO	8	7.5	T6	3	200	200	300	1
53	B	28	M	53009	158	65	I	136	80	110	NO	8.5	8.8	T8	3	210	160	320	1
54	B	29	F	4319	164	63	II	128	78	108	NO	9	9.5	T4	2	220	200	300	1
55	B	34	M	8614	156	58	I	126	74	110	NO	10	8	T6	3	240	240	310	2
56	B	36	M	7493	172	55	I	118	72	106	YES	8.5	8.6	T6	3	200	200	280	1
57	B	34	F	10012	198	59	I	116	74	90	YES	8	8.8	T6	2	210	190	310	1
58	B	35	M	53012	154	61	I	120	78	88	YES	9	8.5	T8	3	280	200	300	1
59	B	33	M	4753	160	55	I	116	74	92	YES	7.5	8	T6	3	220	200	280	1
60	B	32	M	6192	175	72	II	120	78	104	NO	7.5	10	T6	3	240	180	300	1

S.NO	Group	Age	Sex	IP NO.	Ht	Wt	ASA	BP - S	BP-D	MIN BP-S	Vaso pressor	OSB	OMB	MSL	Sed Score	DSB	DMB	PFI	Rescue No.
61	C	41	M	55003	170	60	I	130	90	90	YES	4	7	T4	3	240	200	480	1
62	C	23	M	47753	168	60	I	120	80	100	NO	5	7.5	T4	3	300	240	480	1
63	C	42	F	48413	155	50	I	130	90	100	NO	5	7	T4	3	240	200	420	1
64	C	53	M	39180	160	60	I	110	70	106	NO	4	6.5	T6	3	250	240	480	1
65	C	35	M	50084	165	50	I	112	86	98	NO	3.5	7	T4	3	280	200	420	1
66	C	51	M	36794	160	65	I	142	80	80	YES	3.8	7	T4	2	300	240	900	1
67	C	51	M	38608	165	66	II	130	90	82	YES	4	7.5	T4	3	300	220	720	1
68	C	53	M	2896	168	55	I	126	84	90	YES	5	6	T4	3	300	180	480	1
69	C	61	M	8441	169	65	II	136	82	92	YES	4	6.5	T6	2	300	220	480	1
70	C	55	F	34278	173	76	I	130	80	90	NO	3.5	7	T4	3	240	200	420	1
71	C	23	M	49224	158	53	II	126	80	100	NO	3	7.5	T6	3	240	200	360	1
72	C	41	M	45493	170	58	I	112	76	104	NO	4	6.5	T4	3	240	180	420	1
73	C	32	M	47266	157	59	II	110	78	110	NO	3.5	7	T4	3	240	200	480	1
74	C	24	M	3440	169	72	I	106	80	104	NO	4	7.5	T4	3	300	220	360	1
75	C	43	M	36506	159	73	II	120	78	102	NO	3.8	7	T4	2	360	240	900	1
76	C	35	M	56012	160	65	I	120	70	90	YES	4	7.5	T4	3	360	240	480	1
77	C	43	M	35079	165	76	I	128	80	92	YES	4	6.5	T4	3	240	200	360	1
78	C	52	M	39675	170	72	I	130	90	90	YES	5	7	T6	3	200	180	480	1
79	C	43	F	50167	160	55	I	126	82	90	YES	3.5	7.5	T4	3	240	160	420	1
80	C	54	M	50241	158	58	I	140	86	86	YES	4	7	T4	3	200	180	420	1
81	C	34	M	52047	163	50	I	128	80	92	YES	3.5	7.5	T2	3	300	200	480	1
82	C	31	M	50076	172	68	I	130	78	88	NO	4	7	T4	2	240	220	360	1
83	C	42	M	52113	160	64	I	128	68	104	NO	4	6	T2	2	280	240	390	1
84	C	43	M	50019	158	60	I	126	90	102	NO	3.8	6.5	T4	3	300	220	420	1
85	C	25	M	54855	160	65	I	106	80	100	NO	3.5	7	T6	2	240	200	400	1
86	C	41	F	50013	170	60	I	112	78	104	NO	3.5	6.5	T4	3	200	180	380	1
87	C	43	M	50019	165	70	I	108	70	82	YES	3.5	6	T2	3	240	200	360	1
88	C	52	F	50632	153	65	I	116	72	102	NO	3.5	6	T4	2	280	220	540	1
89	C	53	M	4963	175	68	I	115	72	88	YES	3.8	5.5	T4	3	300	240	420	1
90	C	31	M	5128	172	68	I	114	74	90	YES	4	5.5	T6	3	240	200	480	1